SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ipramol Steri-Neb 0.5mg / 2.5mg per 2.5ml Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5 ml ampoule contains 0.5 mg ipratropium bromide (as the monohydrate) and 2.5 mg salbutamol (as the sulfate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.

A low density polyethylene ampoule containing a colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ipramol Steri-Neb is indicated in adults, adolescents and children aged 12 years and above.

Ipramol Steri-Neb is indicated for the management of bronchospasm in patients suffering from chronic obstructive pulmonary disease (COPD) who require regular treatment with both ipratropium bromide and salbutamol.

4.2 Posology and method of administration

In situations of acute dyspnea (difficulty breathing) or rapid worsening of dyspnea, patients should be advised to immediately consult a doctor or the nearest hospital if additional inhalations of Ipramol Steri-Neb do not produce adequate improvement.

Posology

Adults (including elderly patients and children over 12 years): The content of one ampoule three or four times daily.

Ipramol Steri-Neb has not been studied in patients with liver or kidney failure and should be used with caution in these patient populations.

Paediatric population

The safety and efficacy of Ipramol Steri-Neb in children aged below 12 years have not been established.

Method of administration

Inhalation use.
Ipramol Steri-Neb may be administered from a suitable nebuliser or an intermittent positive pressure ventilator after the single dose ampoule has been opened and its contents transferred to the nebuliser chamber. Administration should be in accordance with the manufacturer's instructions for the devices. The solution in the single dose ampoules is intended for inhalation use only and should not be taken orally or administered parenterally.

i. Prepare the nebuliser by following the manufacturer's instructions and the advice of your doctor.

ii. Carefully separate a new ampoule from the strip. Never use an ampoule that has been opened already.

iii. Open the ampoule by simply twisting off the top always taking care to hold it in an upright position.

iv. Unless otherwise instructed by your doctor, squeeze all the contents of the plastic ampoule into the nebuliser chamber.

v. Assemble the nebuliser and use it as directed by your doctor. The duration of treatment for the inhalation of a complete dose is usually between five and 15 minutes.

vi. After nebulisation clean the nebuliser according to the manufacturer's instructions. It is important that the nebuliser is kept clean.

As the single dose units contain no preservatives it is important that the contents are used immediately after opening and a fresh ampoule is used for each administration to avoid microbial contamination. Partly used, opened or damaged single dose units should be discarded.

Any solution remaining in the nebuliser chamber should be discarded.

It is strongly recommended that Ipramol Steri-Neb should not be mixed with other drugs in the same nebuliser

4.3 Contraindications

- Hypersensitivity to the active substances or to atropine and its derivatives or to any of the excipients listed in section 6.1.
- Hypertrophic obstructive cardiomyopathy
- Tachyarrhythmia.

4.4 Special warnings and precautions for use

Ipramol Steri-Neb should not be used in children (see section 4.2).

Patients should be instructed to consult a doctor immediately in the event of acute, rapidly worsening dyspnoea or if a reduced response to treatment becomes apparent.

Immediate hypersensitivity reactions may occur after administration as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

There are also rare reports of a number of ocular complications when aerosolised ipratropium bromide, either alone or in combination with a $beta_2$-adrenergic agonist, has been inadvertently sprayed into the eye. Patients must therefore be instructed in the correct use of Ipramol Steri-Neb with their nebuliser and must be warned not to allow the solution or mist to enter the eyes. To avoid inadvertent entry of drug into the eye, it is preferable to administer the nebulised suspension using a mouthpiece rather than a face mask.

Such ocular complications may include acute angle glaucoma, mydriasis, blurring of vision, increased intraocular pressure, eye pain and narrow-angle glaucoma. Patients who may be susceptible to glaucoma should be warned specifically about the need for ocular protection. Antiglaucoma therapy is effective in the prevention of acute narrow-angle glaucoma in susceptible individuals.

Eye pain or discomfort, blurred vision, visual halos or coloured spots together with red eyes from conjunctival congestion or corneal oedema may be manifestations of acute narrow-angle glaucoma. If a combination of these symptoms develops, treatment with miotic eye drops should be initiated and the patient should seek specialist advice immediately.

In the following conditions Ipramol Steri-Neb should only be used after careful assessment of risk/benefit: inadequately controlled diabetes mellitus, recent myocardial infarction and/or severe organic heart or vascular disorders, hyperthyroidism, phaeochromocytoma, intestinal obstruction, prostatic hypertrophy, bladder outflow obstruction and risk of narrow-angle glaucoma.

Caution should be exercised when Ipramol Steri-Neb is used by patients with cardiac disease (severe heart disease, ischaemic disease, arrhythmias). Patients should be advised if they experience chest pain and or dyspnoea that they should contact their emergency services.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with beta-agonists. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmias or severe heart failure) who are receiving salbutamol for respiratory disease should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be either respiratory or cardiac in origin.

Potentially serious hypokalaemia may result from $beta_2$-agonist therapy. Particular caution is advised in severe airway obstruction, as this effect may be potentiated by concomitant treatment with xanthine derivatives, diuretics and steroids. Hypokalaemia can bring about increased sensitivity to arrhythmias in patients being treated with digoxin. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm. It is recommended that serum levels of potassium are monitored in such situations.

Patients with cystic fibrosis may be more prone to disturbances in gastrointestinal motility and therefore ipratropium bromide, as with other anticholinergics, should be used with caution in these patients.

As with other inhalation therapy there is a risk of inhalation-induced bronchoconstriction or paradoxical bronchospasm. If this occurs the patient will experience an immediate increase in wheezing and shortness of breath after dosing, which should be treated straightaway with an alternative presentation or different fast-acting inhaled bronchodilator. Ipramol Steri-Neb should be discontinued immediately, the patient should be assessed and, if necessary, alternative therapy instituted.

If it is necessary to use higher doses than recommended to control the symptoms of bronchoconstriction (or bronchospasm) the patient's treatment plan should be reassessed.

Lactic acidosis has been reported in association with high therapeutic doses of intravenous and nebulised short-acting beta-agonist therapy, mainly in patients being treated for an acute exacerbation of bronchospasm in severe asthma or chronic obstructive pulmonary disease (see section 4.8 and 4.9). Increase in lactate levels may lead to dyspnoea and compensatory hyperventilation, which could be misinterpreted as a sign of asthma treatment failure and lead to inappropriate intensification of short-acting beta-agonist treatment. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting.

The use of Ipramol Steri-Neb may lead to positive results with regards to salbutamol in tests for non clinical substance abuse, e.g. in the context of athletic performance enhancement (doping).

<u>Paediatric population</u>

Ipramol Steri-Neb should not be used in children below 12 years (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use of corticosteroids, beta2-adrenoceptor agonists, anticholinergics and xanthine derivatives may enhance the effect of Ipramol Steri-Neb on airway function and may increase the severity of side effects. Due to opposing pharmacodynamic interaction with the salbutamol element, a potentially serious reduction in effect may occur during concurrent administration of beta-blockers such as propranolol.

Salbutamol should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of the $beta_2$ adrenoceptor agonist may be enhanced.

Inhalation of anaesthetics containing halogenated hydrocarbons, e.g. halothane, trichloroethylene and enflurane, may increase the susceptibility to cardiovascular side effects of $beta_2$-agonists, which should therefore be monitored closely. Alternatively discontinuation of Ipramol Steri-Neb prior to surgical operation should be considered.

Potentially serious hypokalaemia may result from beta2-agonist therapy. Particular caution is advised in severe airway obstruction, as this effect may be potentiated by concomitant treatment with xanthine derivatives, diuretics and steroids. Potentially serious arrhythmias may occur during concomitant administration of digoxin and Ipramol Steri-Neb. The interaction risk is aggravated by hypokalaemia and should be monitored regularly. Hypokalaemia can bring about increased sensitivity to arrhythmias in patients being treated with digoxin.

The effect of other anticholinergic products may be potentiated.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of Ipramol Steri-Neb during pregnancy has not yet been established. The inhibitory effect of Ipramol Steri-Neb on uterine contraction should be taken into consideration. The benefits of using Ipramol Steri-Neb during a confirmed or suspected pregnancy should be weighed against the possible harm to the foetus. The usual precautions should be taken regarding the use of medicines in pregnancy, especially during the first trimester.
For ipratropium bromide, preclinical studies have not demonstrated embryotoxic or teratogenic effects after inhalation or intranasal application at doses considerably higher than those recommended in man. For salbutamol sulphate, non-inhalation preclinical studies indicated no direct or indirect harmful effects unless the maximum recommended inhalation dose for adults was exceeded (see section 5.3).

Breastfeeding

It is not known whether ipratropium bromide and salbutamol sulphate are excreted in breast milk. Although lipid insoluble quaternary cations pass into breast milk, it is considered unlikely that ipratropium bromide will reach the infant to any significant extent when administered by inhalation. However, as many drugs are eliminated in breast milk, precautions should be taken when Ipramol Steri-Neb is given to breast-feeding mothers.

Fertility
No studies on the effects of Ipramol Steri-Neb on human fertility have been performed. Pre-clinical studies with ipratropium bromide and salbutamol did not show any adverse effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, patients should be advised that they may experience undesirable effects such as dizziness, accommodation disorders, mydriasis and blurred vision during treatment with Ipramol Steri-Neb. If patients experience the above mentioned side effects, they should avoid potentially hazardous tasks such as driving or operating machines.

4.8 Undesirable effects

Many of the undesirable effects described can be attributed to the anticholinergic and beta-2 sympathomimetic properties of Ipratropium/Salbutamol. As with all inhalation therapies, Ipramol Steri-Neb may cause symptoms of local irritation. Adverse reactions were identified from data obtained through clinical trials and pharmacovigilance activities in the post-approval phase of the drug.
The most frequently reported undesirable effects in the clinical trials were headache, throat irritation, cough, dry mouth, gastrointestinal motility disturbances (including constipation, diarrhoea and vomiting), nausea and dizziness.

Based on the MedDRA system organ class and frequencies, adverse events are listed in the table below.

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to < 1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

System organ class	**Frequency**	**Symptom**
Immune system disorders	Rare	Anaphylactic reaction Hypersensitivity including angioedema of the tongue, lips and face
Metabolism and nutritional disorders	Rare Not known	Hypokalaemia Lactic acidosis (see section

		4.4)
Psychiatric disorders	Uncommon Rare	Restlessness Memory disorders, mental disorders, anxiety, hyperactivity in children
Nervous system disorders	Uncommon	Headache, Dizziness, Tremor
	Rare	Sleep disturbances
Eye disorders	Rare	Accommodation disorders Corneal edema Pain in the eye Mydriasis Increased intraocular pressure Glaucoma Blurred vision Conjunctival hyperemia Visual halos
Cardiac disorders	Uncommon Rare	Palpitations, tachycardia Arrhythmias Peripheral vasodilatation Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) and coronary ischaemic disease. Myocardial ischaemia (see section 4.4)
Respiratory, thoracic and mediastinal disorders	Uncommon Rare	Cough Dysphonia Dry throat Bronchospasm Laryngospasm Dyspnoea Paradoxical bronchospasm (i.e., inhalation-induced bronchospasm) Pharyngeal edema
Gastrointestinal disorders	Uncommon Rare	Dry mouth Nausea Throat irritations Diarrhoea Vomiting Obstipation

		Motility disturbances Edema of the mouth Stomatitis
Skin and subcutaneous tissue disorders	Rare	RashUrticaria, Pruritus Hyperhidrosis Angioedema
Musculoskeletal, connective tissue and bone disorders	Rare	Myalgia Muscle cramps Muscle weakness
Renal and urinary disorders	Rare	Urinary retention
General disorders and administration site conditions	Rare	Asthenia
Investigations	Uncommon Rare	Systolic blood pressure increased Diastolic blood pressure decreased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

The effects of an overdose can be expected to be mainly related to salbutamol.
The expected symptoms of an overdose are the same as those of excessive beta-adrenergic stimulation, the most important being tachycardia, Palpitations, anginal pain, hypertension, hypotension, hypokalaemia, tachycardia, arrhythmia, chest pain, tremor, flushing, restlessness and dizziness. Patients should therefore be monitored closely for the potential unwanted effects from overdosage of salbutamol.

Metabolic acidosis has also been observed with overdosage of salbutamol, including lactic acidosis which has been reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy, therefore monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of tachypnea despite resolution of other signs of bronchospasm such as wheezing/pyrexia) may be indicated in the setting of overdose.

Hypokalaemia may occur following overdose with salbutamol and therefore serum potassium levels should be monitored.

The expected effects of an overdose with ipratropium bromide (such as dry mouth, visual accommodation disturbances) are mild and transient in nature, taking into account the wide therapeutic range and topical administration.

Treatment
Sedatives, tranquilizers, in severe cases intensive treatment.
Beta-receptor blockers, preferably selective for beta 1, are suitable as specific antidotes; however, possible increased bronchial obstruction must be taken into consideration and the dose must be adjusted carefully in patients suffering from bronchial asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Salbutamol and Ipratropium bromide for obstructive airway disease ATC code: R03A L02.

Mechanism of action
Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasimpaticolytic) properties. In preclinical studies, it seems to inhibit vague-mediated reflexes by antagonizing the action of acetylcholine, the transmitting agent released by the vagus nerve. Anticholinergics prevent the increase of intracellular concentration of calcium ion, which is caused by the interaction of acetylcholine with the muscarinic receptor of the smooth muscle of the bronchi. The release of calcium ion is mediated by the system of the second messenger consisting of inositol triphosphate (IP3) and diacylglycerol (DAG).
Bronchodilation that occurs after inhalation of ipratropium bromide is mainly local and specific in nature in the lung and non-systemic.

Salbutamol is a $beta_2$-adrenoceptor agonist, which acts on airway smooth muscle resulting in relaxation. Salbutamol relaxes all smooth muscle from the trachea to the terminal bronchioles and protects against bronchoconstrictor challenges.

Ipramol Steri-Neb provides the simultaneous delivery of ipratropium bromide and salbutamol sulfate producing effects on both muscarinic and $beta_2$-adrenoceptor receptors in the lung. This provides enhanced bronchodilatation over that provided by each drug alone.

Controlled studies conducted in patients with reversible bronchospasmo have shown that Ipratropium/Salbutamol has a bronchodilator effect greater than the effect of its components, without potentiating undesirable effects.

5.2 Pharmacokinetic properties

From a pharmacokinetic perspective, the efficacy observed in clinical trials conducted with Ipratropium/Salbutamol results from a local effect on the lungs after inhalation. After inhalation 10 to 39% of the dose is usually deposited in the lungs, depending on the formulation, inhalation technique and device, while the remaining dose is deposited in the mouth of the administration device, mouth and upper part of the respiratory tract (oropharynx).
The dose deposited in the lungs reaches circulation quickly (in minutes). The amount of active substance deposited in the oropharynx is slowly swallowed and passes through the gastrointestinal tract. Consequently, systemic exposure is a function of oral and pulmonary bioavailability.

Ipratropium
Cumulative renal excretion (0-24 h) of ipratropium (related compound) is approximately up to 46% of an intravenously administered dose, less than 1% of an oral dose and approximately 3-4% of an inward dosed dose. Based on these data, the total systemic bioavailability of oral and inward doses of ipratropium bromide is estimated at 2% and 7 to 9%, respectively. Taking this into account, dose of swallowed ipratropium bromide do not contribute significantly to systemic exposure.
The kinetic parameters describing the arrangement of ipratropium were calculated from plasma concentrations after intravenous administration. A rapid biphasic decline in plasma concentrations is observed. The apparent volume of distribution at steady state (Vdss) is approximately 176 L (≈ 2.4 L/kg). The drug binds minimally (less than 20%) plasma proteins. Pre-clinical studies with rats and dogs have revealed that quaternary ipratropium amine does not cross the blood brain barrier.
The half-life of the terminal phase of elimination is approximately 1.6 hours. Ipratropium has a total clearance of 2.3 L/min and renal clearance of 0.9 L/min. After intravenous administration approximately 60% of the dose is metabolized, mostly in the liver by oxidation.
In a study of variation of excretion, cumulative renal excretion (6 days) of drug-related radioactivity (including related compound and all metabolites) corresponded to 72.1% of the dose after intravenous administration, 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted in feces was 6.3% after intravenous administration, 88.5% after oral administration and 69.4% after inhalation.
Regarding the excretion of drug-related radioactivity after intravenous administration, the main excretion occurs through the kidneys. The elimination half-life of drug-related radioactivity (related compound and metabolites) is 3.6 hours. The main urinary metabolites bind weakly to the muscarinic receptor and are considered ineffective.

Salbutamol
Salbutamol is rapidly and completely absorbed after oral administration by both inhalation and gastric routes and has an oral bioavailability of approximately 50%. The mean peak plasma concentration for salbutamol, 492 pg/ml, occurs within three hours of inhalation of Ipramol Steri-Neb. Following this single inhalation administration, approximately 27% of the estimated oral dose of the device is excreted unchanged in the 24-hour urine. Kinetic parameters were calculated from plasma concentrations after intravenous administration. The apparent volume of distribution (Vz) is approximately 156 L (≈ 2.5 L/kg).
Only 8% of the drug binds to plasma proteins. Salbutamol crosses the blood-brain barrier reaching concentrations corresponding to about 5% of plasma concentrations.

The mean terminal half-life is approximately 4 hours with a mean total clearance of 480 mL/min and a mean renal clearance of 291ml/min.
Salbutamol is metabolised by conjugation to salbutamol 4'-O-sulphate. The R(-) enantiomer of salbutamol (levosalbutamol) is preferentially metabolised, and consequently eliminated from the body, more rapidly than the S(+) enantiomer. After intravenous administration, urinary excretion was complete after approximately 24 hours. Most of the dose was excreted as the related compound (64.2%) and 12.0% was excreted as sulphate conjugate. After oral administration the urinary excretion of unchanged drug and sulphate conjugate was 31.8% and 48.2% of the dose, respectively.

Co-administration of ipratropium bromide and salbutamol sulfate does not potentiate the systemic absorption of either component, so the additive effect of Ipramol Steri-Neb is due to the combined local effect of both drugs on the lung after inhalation.

5.3 Preclinical safety data

The acute toxicity of ipratropium bromide/salbutamol after administration of a single inhalation was tested in rats and dogs. Up to the highest technically appropriate dose (rat: 887/5397 micrograms/kg ipratropium bromide/salbutamol, dog: 164/861 micrograms/kg ipratropium bromide/salbutamol), no systemic toxic effects were seen and the combination was well tolerated locally. The approximate LD50 after intravenous administration was calculated for the substances individually and was between 12 and 20 mg/Kg for ipratropium bromide and between 60 and 73 mg/Kg for salbutamol sulphate, depending on the species tested (mouse, rat, dog).

Two 13-week inhalation toxicity studies were conducted in rats and dogs with the combination of ipratropium bromide and salbutamol sulphate. In these studies, the heart proved to be the target organ. In the rat, at dosages of 34/197 to 354.5/2604 micrograms/kg/day of ipratropium bromide/salbutamol sulphate, there was a dose-dependent increase in heart weight without, however, any correlated histopathological changes. In the dog, at doses of 32/198 to 129/790 micrograms/kg/day of ipratropium bromide/salbutamol sulphate, slight increases in heart rhythms and, for the higher doses, histopathologically detectable scarring and/or fibrosis in the left ventricular papillary muscle.

The cardiovascular results obtained in the above mentioned studies are well known with beta-adrenergics such as salbutamol. The toxicological profile of ipratropium bromide has also been well known for many years and is characterised by typical anticholinergic effects such as dryness of the mucous membranes of the head, mydriasis, dry kerato-conjunctivitis (dry eye) in dogs only, reduced tone and inhibition of motility of the gastrointestinal tract (rat).

Reproduction toxicology studies exist for the two individual components of ipratropium bromide/salbutamol. Salbutamol sulfate caused cleft palate in the mouse at high subcutaneous doses, starting at doses within the range of the maximum recommended inhalation dose for adults (based on mg/m2). However, this phenomenon is well known and also occurs after administration of other beta-

adrenergic compounds. It is now assumed that this effect is caused by an increase in maternal corticosterone level and should be interpreted as a result of stress, not relevant for other species. Apart from these results, studies conducted with salbutamol sulphate and ipratropium bromide revealed only marginal effects, if any, on embryos, foetuses and pups, and these effects occurred at maternal-toxic doses.

Both substances have been tested individually in numerous *in vivo* and *in vitro* genotoxicity tests. Neither salbutamol sulphate nor ipratropium bromide has shown any evidence of mutagenic properties. Additionally, ipratropium bromide/salbutamol has not demonstrated genotoxic activity in *in vitro* assays.

Salbutamol sulphate and ipratropium bromide have been tested individually for neoplastic properties in several carcinogenesis studies. After oral administration of salbutamol sulphate to rats, but not mice, hamsters and dogs, an increased incidence of leiomyomas of the mesovarium was observed at dosages about ≥20 times higher than the maximum recommended inhaled dose for adults. The development of leiomyomas could be prevented by simultaneous administration of beta-blockers. These results were considered to be species-specific and therefore without clinical relevance, consequently not leading to any restriction of the clinical use of salbutamol sulphate.

Ipratropium bromide has not been shown to have carcinogenic potential when tested orally in mice and rats. No evidence of immunotoxicological effects caused by ipratropium bromide/salbutamol individually was found.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Dilute Hydrochloric Acid for pH adjustment
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not freeze. Store below 25°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Low Density Polyethylene Ampoule called a Steri-Neb containing 2.5 ml of solution, formed into strips of 5 and packed into a foil overwrap pouch that is then packed into cardboard cartons containing 5, 10, 15, 20, 25, 30, 40, 50 or 60 Steri-Nebs and 2 x 30 ampoule-pack, then packed into a cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Since the single dose units contain no preservatives, it is important that the contents are used soon after opening and a fresh ampoule is used for each administration to avoid microbial contamination. Partly used, opened or damaged single dose units should be disposed of in accordance with local requirements.

After nebulisation, clean the nebuliser according to the manufacturer's instructions as follows: the oral mouthpiece should be cleaned with hot water. If soap is used, the mouthpiece should be rinsed thoroughly with water. When dry, the cap should be replaced on the mouthpiece.

7. MARKETING AUTHORISATION HOLDER

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